Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Dolutegravir (DTG, Tivicay) (Last updated Sept. 8, 2016; last reviewed Sept. 8, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Tablet: 10 mg, 25 mg, and 50 mg

Fixed-Dose Combination Tablet:

- [*Triumeq*] Abacavir 600 mg plus dolutegravir 50 mg plus lamivudine 300 mg

Dosing Recommendations

Neonate/Infant Dose:

- Not approved for use in neonates/infants

Children Weighing ≥30 to <40 kg:

- Not FDA approved for use in children weighing <30 kg.
- A clinical trial in ARV treatment-experienced (but INSTI-naive children) weighing <30 kg is underway (see text).

Body weight (kg)	Dose[a] (mg/day)	Tablet Number	Dosing Frequency	Tablet Size (mg)
>40	50	1	Once daily	50
30 to <40	35	2	Once daily	10 plus 25

[a] These doses are for children who are ARV-naive or ARV-experienced (but INSTI-naive) and who are not being treated with UGT1A1/CYP3A inducers

Note: When ordering dolutegravir 10 mg or 25 mg tablets have the pharmacy call their drug wholesaler and tell the drug wholesaler to order directly from the GSK distribution center. The GSK distribution center will ship the formulation directly to the pharmacy.

Children and Adolescents (Weighing ≥40 kg) and Adult Dose:

Population	Recommended Dose
Treatment-naive or treatment-experienced/(INSTI)-naive	50 mg once daily
Treatment-naive or treatment-experienced/ INSTI-naive when co-administered with the following potent UGT1A/CYP3A inducers: efavirenz, fosamprenavir/ ritonavir, tipranavir/ritonavir, or rifampin	50 mg twice daily
INSTI-experienced with any INSTI-associated resistance substitutions or clinically suspected INSTI resistance[a]	50 mg twice daily

[a] Combinations that do not include metabolic inducers should be considered where possible.

Selected Adverse Events

- Insomnia
- Headache
- Hypersensitivity reactions including rash, constitutional symptoms, and organ dysfunction (including liver injury) have been reported rarely.

Special Instructions

- May be taken without regard to meals
- Should be taken 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral iron supplements, oral calcium supplements, or buffered medications
- The efficacy of 50 mg dolutegravir twice daily is reduced in patients with certain combinations of INSTI-resistance mutations (see Resistance section below).

Metabolism/Elimination

- UGT1A1 and cytochrome P450 (CYP) 3A substrate
- Dosing in patients with hepatic impairment: No dose adjustment is necessary in patients with mild or moderate hepatic impairment. Because of lack of data, dolutegravir is not recommended in patients with severe hepatic impairment.
- Dolutegravir decreases tubular secretion of creatinine and slightly increases measured serum creatinine, but does not affect glomerular filtration.
- Dosing in patients with renal impairment: No dose adjustment is required in INSTI-naive patients with mild, moderate, or severe renal impairment or in INSTI-experienced patients with mild or moderate renal impairment.

Combination Tablet
[Triumeq] Abacavir plus Dolutegravir plus Lamivudine:

Adolescent (Weighing ≥40 kg) and Adult Dose:

- 1 tablet once daily
- For use in patients who are ARV treatment-naive or treatment-experienced (but INSTI-naive) and not being treated with UGT1A1/CYP3A inducers
- Use dolutegravir with caution in INSTI-experienced patients with severe renal impairment (creatinine clearance <30 mL/min) because dolutegravir concentrations will be decreased (the cause of this decrease is unknown).

Drug Interactions (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents and http://www.hiv-druginteractions.org/)

- *Metabolism:* Dolutegravir is a UGT1A1 and CYP3A substrate and may require dosage adjustments when administered with UGT1A1 or CYP3A-modulating medications. Because etravirine significantly reduces plasma concentrations of dolutegravir, dolutegravir should not be administered with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir, which counteracts this effect on dolutegravir concentrations. Dolutegravir should not be administered with nevirapine because of insufficient data.
- Before dolutegravir is administered, a patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities

- *More common:* Insomnia and headache
- *Less common (more severe):* Hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction, neuropsychiatric symptoms.

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10), and the Stanford University HIV Drug Resistance database offers a discussion of integrase strand transfer inhibitor (INSTI) mutations (http://hivdb.stanford.edu/DR/). The efficacy of 50 mg dolutegravir twice daily is reduced in patients with INSTI-resistance Q148 substitution plus two or more additional INSTI-resistance mutations: T66A, L74I/M, E138A/K/T, G140SA/C, Y143R/C/H, E157Q, G163S/E/K/Q, or G193E/R.

Pediatric Use

Approval

Dolutegravir is Food and Drug Administration (FDA)-approved in combination with other antiretroviral drugs for children, weighing at least 30 kg, and who are treatment-naive or treatment-experienced but INSTI-naive.[1]

Efficacy and Pharmacokinetics

IMPAACT P1093 is an ongoing open-label trial of HIV-infected children with the plan to enroll down to age 4 weeks. FDA approval of dolutegravir down to age 12 years/40 kg was based on data from 23 treatment-experienced, INSTI-naive adolescents.[2] Intensive pharmacokinetic (PK) evaluations were performed on the first 10 participants (9 weighing ≥40 kg and receiving 50 mg, 1 weighing 37 kg and receiving 35 mg) and revealed exposures comparable to those seen in adults receiving 50 mg once daily. Nine of 10 participants achieved HIV RNA concentration <400 copies/mL at week 4 (optimal background therapy was added 5 to 10

days after dolutegravir was started). An additional 13 participants were then enrolled for evaluation of long-term outcomes. At 48 weeks, 61% had achieved HIV RNA concentration <50 copies/mL. No safety or tolerability concerns were identified. By week 144, 39% and 30% had achieved HIV RNA concentrations <400 and <50 copies/mL, respectively.[3] All who experienced virologic failure were nonadherent. In addition, children aged ≥6 to <12 years are undergoing PK and longer-term follow up in P1093, with those weighing ≥30 to <40 kg receiving the 35 mg dose and those weighing ≥40 kg using the 50 mg dose. To date, data from 11 participants have demonstrated a favorable safety profile, adequate PK, and virologic efficacy through 24 weeks.[2,4] This has led to FDA approval of the lower strength tablets for HIV-infected children as young as 6 years and with body weight as low as 30 kg. An oral pediatric granule formulation is also being studied. Doses for smaller children are under investigation in P1093.

Pharmacokinetics of Dolutegravir in Adult and Pediatric Studies

Population of Study	Weight (kg)	Dose (mg/day)	Tablets	Tablet Size (mg)	Dosing Frequency	Dose for Lowest Weight in Weight Band (mg/kg)	Trough Plasma Concentration[a] mcg/mL
Adults with Prior INSTI Treatment	>40	100	2	50	Twice daily	2.5	2.12 (47)[b]
Adults without Prior INSTI Treatment	≥40	50	1	50	Once daily	1.25	1.11 (46)
Children without Prior INSTI Treatment (N = 14)	≥40	50	1	50	Once daily	1.25	0.99 (66)
Children without Prior INSTI Treatment (N = 3)	30 to <40	35	2	10 plus 25	Once daily	1.17	1.33 (93)

[a] Source: Dolutegravir [package insert]. Food and Drug Administration. 2016. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204790Orig1s008lbl.pdf

[b] Geometric mean (percent coefficient of variation)

Note: Recommendations for 100 mg/day are for adults in special circumstances using 50 mg twice daily (see product label or text above).

References

1. Dolutegravir [package insert]. Food and Drug Administration. 2016. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204790Orig1s008lbl.pdf. Accessed August 29, 2016.
2. Viani RM, Alvero C, Fenton T, et al. Safety, pharmacokinetics and efficacy of dolutegravir in treatment-experienced HIV-1 infected adolescents: 48-week results from IMPAACT P1093. *Pediatr Infect Dis J*. 2015. Available at http://www.ncbi.nlm.nih.gov/pubmed/26244832.
3. Viani R, Alvero C, Fenton T, et al. Long-term safety and efficacy of dolutegravir in HIV treatment-experienced adolescents. Presented at: Infectious Disease Week. 2015. San Diego, CA.
4. Viani R, Carmelita A, Fenton T, et al. Safety, pharmacokinetics and efficacy of dolutegravir in treatment-experienced HIV+ children. Presented at: 21st Conference on Retroviruses and Opportunistic Infections. 2014. Boston, MA.